

## Review article

# Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods



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## ABSTRACT

Variation in maternal care can lead to divergent developmental trajectories in offspring with implications for neuroendocrine function and behavioral phenotypes. Study of the long-term outcomes associated with mother–infant interactions suggests complex mechanisms linking the experience of variation in maternal care and these neurobiological consequences. Through integration of genetic, molecular, cellular, neuroanatomical, and neuroendocrine approaches, significant advances in our understanding of these complex pathways have been achieved. In this review, we will consider the impact of maternal care on male and female offspring development with a particular focus on the issues of timing and mechanism. Identifying the period of sensitivity to maternal care and the temporal dynamics of the molecular and neuroendocrine changes that are a consequence of maternal care represents a critical step in the study of mechanism.

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## 1. Introduction

Parent–offspring interactions are a critical developmental cue to environmental quality and have the capacity to impact growth, survival, physiology, and behavior. In mammals, biparental care is a relatively rare occurrence and these interactions are primarily through the mother. The capacity of offspring to shift in development in response to the quality of mother–infant interactions may represent an important adaptive pathway that prepares offspring for the conditions of life (Cameron et al., 2005). Our understanding of the adaptive process and mechanisms underlying the effects of maternal care has been advanced by human longitudinal and laboratory animal studies. Overall, these studies have highlighted the impact of mother–infant interactions on multiple neuroendocrine systems, including the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–gonadal axis (HPG), and the mesolimbic dopamine (DA) system (Cameron et al., 2008; Meaney, 2001; Pena et al., 2014). Within these systems, there is evidence for long-term transcriptional activation and repression in association with postnatal maternal care, prompting analyses of the impact of mother–infant interactions on epigenetic processes (Weaver et al., 2004). Epigenetic

mechanisms, such as DNA methylation, post-translational histone modifications, and microRNAs have been implicated in studies of the impact of environmental experiences including nutrition (Lillycrop et al., 2005; Heijmans et al., 2008), toxins (Anway et al., 2006; Kundakovic et al., 2013), stress (Mueller and Bale, 2008; Roth et al., 2011), and social experiences (Hollis et al., 2010; Murgatroyd et al., 2009). Variation in (Weaver et al., 2004) or deprivation of (Murgatroyd et al., 2009; Franklin et al., 2010) maternal care has been demonstrated to induce long-term epigenetic alterations, with implications for the development of neural circuits and the function of these circuits in adulthood.

Plasticity of the brain in response to the quality of mother–infant interactions during the postnatal period suggests the presence of a sensitive period for the development of these systems and their associated physiological and behavioral outcomes. The notion of critical or sensitive periods has a strong foundation within research on sensory systems (Hubel and Wiesel, 1970) and social imprinting (Hess, 1959) and suggests that there are windows of time during development in which experiences may be maximally effective in inducing neurobiological and behavioral change. However, in the case of the influence of maternal care, much of the evidence for a particular window of sensitivity is correlative and cross-fostering studies have primarily focused on dissociating the impact of genetic or prenatal vs. postnatal maternal care influences rather than on identifying postnatal sensitive periods. However, emerging evidence for these periods (Pena et al., 2013; Upton and Sullivan, 2010), highlights the need to integrate

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the study of the temporal dynamics of developmental change when considering the influence of maternal care. Though the long-term effects of maternal care have been relatively well described, the process of change and the intermediary molecular and neurobiological effects that may shape the developing brain have not been systematically explored.

In this review, we will highlight research approaches that have been used to study the impact of maternal care on the developing brain in male and female offspring. We will discuss three specific approaches used primarily in laboratory rodents: (1) the impact of naturally occurring variations in maternal care, (2) communal rearing, and (3) the impact of home-cage disruption. Though there are many other approaches that have been implemented (e.g. neonatal handling, maternal separation), the methodologies we will focus on in this review possess similarities in their effects on both the quantitative and qualitative aspects of maternal care and are currently incorporating epigenetic analyses. We will describe the literature implicating epigenetic mechanisms in the long-term impact of maternal care within these paradigms, with a particular emphasis on the timing of epigenetic changes. Finally, we will explore the notion of critical or sensitive periods in the effects of maternal care and how current and future research approaches can further our understanding of the fundamental questions of the timing and reversibility of epigenetic and neurobiological impact of maternal care.

## 2. Neurobiological and behavioral impact of variation in maternal care

Decades of research has explored the impact of maternal care on the development of offspring using a variety of observational and experimental approaches to quantify or manipulate the quality of mother–infant interactions. Historically, there has been a particular focus on the impact of disruptions to these interactions leading to the establishment of maternal separation or deprivation approaches in non-human primates (Harlow et al., 1965; Suomi et al., 1976) and rodents (Hofer, 1973; West, 1993). However, longitudinal studies in humans have implicated maternal sensitivity to offspring cues and parental warmth to early- and later-life behavioral and neurobiological outcomes (Hane et al., 2010; Narita et al., 2010). Thus, variation in care rather than deprivation of care may be an appropriate strategy for studying long-term neurodevelopmental programming. Here, we will consider three approaches in which the impact of this variation can be examined in a laboratory setting: (1) naturally occurring variations in maternal care, (2) communal rearing, and (3) home-cage disruption.

### 2.1. Natural variations in maternal care

Across species, there are naturally occurring variations in maternal care that predict long-term neurobiological and behavioral phenotypes in offspring. In humans, maternal sensitivity to infant cues is a normally distributed behavior, and infants that have experienced low vs. high maternal sensitivity exhibit increased indices of fearfulness, reduced positive joint attention, increased negative affect, increased aggression, social inhibition and greater right frontal electroencephalographic asymmetry (Hane et al., 2010; Hane and Fox, 2006). In non-human primates, high levels of postnatal over-protectiveness (high levels of approach, contact and restraint) in *Chlorocebus pygerythrus* is associated with reduced exploratory behavior in juvenile offspring (Fairbanks and McGuire, 1988) and the experience of higher rates of rejection (from mothers, fathers, and siblings) in *Callithrix geoffroyi* predicts elevated stress-induced urinary cortisol levels (Birnie et al., 2013). Individual differences in maternal behavior in rodents

emerge even within the controlled conditions of the laboratory and form the basis of variation in offspring brain and behavior. In laboratory rats (*Rattus norvegicus*), observations of home-cage maternal behavior indicate that the experience of low vs. high licking/grooming (LG) from mothers during the postnatal period results in prolonged elevations in plasma corticosterone following stress exposure (Liu et al., 1997), reduced exploration of novel or anxiogenic environments (Caldji et al., 1998), increased fearfulness (Menard et al., 2004), and impairments in learning and memory (Liu et al., 2000) in adult male Long-Evans rat offspring. Adult female offspring of low- compared to high-LG rat dams display increased sexual behavior (Cameron et al., 2008) and reduced maternal behavior (Francis et al., 1999). It should be noted that this methodological approach does not typically assess the LG received by individual pups but rather the overall LG “style” of the dam. There is significant stability in LG behavior by dams across subsequent litters and following cross-fostering (Champagne et al., 2003), suggesting that pup characteristics likely do not account for LG status. However, there is considerable within-litter variation in the receipt of LG by pups, such that some pups receive more LG and some pups receive less LG regardless of the LG status of the dam (Pan et al., 2014; van Hasselt et al., 2012). For example, sex differences in the receipt of LG have been observed in Long-Evans rats, such that males receive higher levels of LG than females (Moore and Morelli, 1979). This variation likely contributes to within-litter variation and sex differences in phenotype and the paradoxical findings regarding the effects of between-litter vs. within-litter variation in LG (Pan et al., 2014; Ragan et al., 2012).

The behavioral and physiological impact of maternal LG is mediated by alterations in the function of several neural/neuroendocrine systems. In male offspring, the focus of analyses has been on gene/protein targets implicated in stress reactivity, fear responses, and cognition. The increased stress reactivity of adult male offspring of low- vs. high-LG Long-Evans rat dams has been attributed to changes in gene expression and protein levels with hypothalamic and hippocampal regions associated with HPA function (see Table 1). Adult male offspring reared by low-LG dams, have elevated corticotrophin releasing factor (CRF) mRNA in the paraventricular nucleus of the hypothalamus (Liu et al., 1997) and decreased protein and mRNA levels of glucocorticoid receptors (GR) within the hippocampus which may account for the increased plasma adrenocorticotrophin (ACTH) and corticosterone levels in low-LG offspring following stress exposure (Liu et al., 1997; Francis et al., 1999). Enhanced fear responses in the offspring of low-LG dams may involve altered expression of subunits within the gamma-aminobutyric acid A receptor (GABA<sub>A</sub>R) in the amygdala and locus coeruleus, decreased hippocampal glutamate decarboxylase 1 (GAD1) mRNA (Zhang et al., 2010), and increased CRH protein levels within the nucleus tractus solitarius (Caldji et al., 1998, 2003). Deficits in learning/memory in the offspring of low-LG dams may be a consequence of several cellular and molecular changes in the medial prefrontal cortex (mPFC) and hippocampus, including decreased protein levels of reelin, synaptophysin, brain-derived neurotrophic factor (BDNF), and neural cell adhesion molecule (NCAM) (Liu et al., 2000; van Hasselt et al., 2012; Smit-Rigter et al., 2009), altered hippocampal expression of subunits within N-methyl-D-aspartate receptor (NMDAR) (Liu et al., 2000; Bagot et al., 2012; Bredy et al., 2004), decreased hippocampal metabotropic glutamate receptor 1 (mGluR1) mRNA (Bagot et al., 2012), decreased hippocampal dendritic complexity (Bagot et al., 2009; Champagne et al., 2008), and decreased excitatory post-synaptic potentials (EPSPs) indicating impaired long-term potentiation (LTP) (Bagot et al., 2009; Bredy et al., 2003). The impact of maternal LG on these outcomes within the hippocampus appears to vary significantly between the dorsal and ventral regions, indicating the regional-specificity of these

**Table 1**  
Impact of low vs. high maternal LG on neuroendocrine outcomes in adult male Long-Evans rats.

Brain region	Effect of low vs. high LG	Reference
mPFC	↓ $\alpha 1$ , ↓ $\alpha 4$ GABA <sub>A</sub> R subunit mRNA ↑ stress-induced dopamine release; ↓ COMT protein ↑ dendritic complexity; ↓ reelin protein levels	Caldji et al. (2003) Zhang et al. (2005) Smit-Rigter et al. (2009)
PVN	↑ CRH mRNA	Liu et al. (1997)
Hippocampus	↓ GR mRNA and protein ↓ MR protein ↑ <i>Nr3c1</i> DNA methylation ↓ H3K9Ac and ↓ NGFI-A binding to <i>Nr3c1</i> promoter ↑ ↓ H3K9Ac and DNA methylation Chr18 ↑ protocadherin mRNA ↓ $\alpha 1$ , ↓ $\beta 3$ GABA <sub>A</sub> R subunit mRNA ↓ GAD1 mRNA ↑ DNA methylation of <i>Gad1</i> promoter ↓ H3K9Ac and ↓ NGFI-A binding to <i>Gad1</i> promoter ↓ reelin mRNA; ↓ ATRX mRNA ↓ acetylcholine release ↓ choline acetyltransferase activity ↓ synaptophysin, ↓ NCAM protein ↑ BAX protein; ↑ apoptosis ↓ neuronal survival ↓ NR1, ↓ NR2A, ↓ NR2B, ↓ GluR1, ↓ GluR3 NMDAR subunit mRNA  ↑ GluN2A, ↑ GluN2B, ↑ GluN1 NMDAR subunit mRNA ↓ EPSPs; ↓ population spike amplitudes ↓ NMDAR binding; ↑ AMPAR binding ↓ reduced dendritic spine density, complexity, and length ↓ BDNF mRNA (exon IX); ↑ immature neurons (DCX) ↑ SCN2A mRNA (dorsal hippocampus only) ↓ mGluR1 mRNA and protein ↑ <i>Grm1</i> promoter DNA methylation ↓ H3K9Ac and H3K4me3 at <i>Grm1</i> promoter	Liu et al. (1997) and Francis et al. (1999) Champagne et al. (2008) Weaver et al. (2004) Weaver et al. (2005) McGowan et al. (2011)  Caldji et al. (2003) Zhang et al. (2010)  Weaver et al. (2005) Liu et al. (2000)  Weaver et al. (2002) Bredy et al. (2003) Liu et al. (2000) Bredy et al. (2004) Bagot et al. (2012) Bredy et al. (2003)  Bagot et al. (2009) and Champagne et al. (2008) van Hasselt et al. (2012) Nguyen et al. (2015) Bagot et al. (2012)
Amygdala	↓ benzodiazepine receptor binding ↓ $\alpha 1$ , ↑ $\alpha 3$ , ↑ $\alpha 4$ , ↓ $\alpha 5$ , ↓ $\beta 2$ , ↓ $\beta 3$ , ↓ $\gamma 1$ , ↓ $\gamma 2$ GABA <sub>A</sub> R subunit mRNA; ↓ $\alpha 1$ , ↓ $\alpha 2$ , $\gamma 2$ GABA <sub>A</sub> R subunit protein ↓ vasopressin V1a receptor binding (central nucleus)	Caldji et al. (1998) and Francis et al. (1999) Caldji et al. (2003)  Francis et al. (2002)
Locus coeruleus	↓ benzodiazepine receptor binding ↓ $\alpha 2$ adrenoreceptor binding ↑ CRH receptor binding ↓ $\alpha 1$ , $\alpha 2$ , ↓ $\beta 2$ , ↓ $\beta 3$ , ↓ $\gamma 2$ GABA <sub>A</sub> R subunit mRNA	Caldji et al. (1998)  Caldji et al. (2003)
Nucleus tractus solitarius	↑ CRH receptor binding	Caldji et al. (1998)

experience-induced effects (Nguyen et al., 2015). Though impairments in cognition have been observed in low- compared to high-LG offspring, under conditions of HPA activation (elevated corticosterone), low-LG males show enhancements in LTP and cognitive performance (Champagne et al., 2008). These findings suggest that the function of these systems may be highly context-dependent, with “optimal” performance for low-LG offspring occurring under conditions of heightened stress and deficits in cognition occurring in these offspring under conditions of minimal stress. The context-dependency of these early life influences fits within a framework of predictive adaptive responses (Bateson et al., 2014), in which developmental plasticity in response to environmental cues (*i.e.* neuroendocrine changes associated with reduced maternal care) prepares individuals for the environmental conditions of later life (*i.e.* a high stress context). Within this framework, the enhanced cognition observed in low-LG offspring under conditions of stress reflects the better match between the early and later life environments.

In contrast to adult male offspring, where outcomes related to stress physiology and cognition have been a primary focus, the study of female offspring of low- vs. high-LG rat dams has typically focused on reproductive behavior (see Table 2). Adult females of low-LG dams do exhibit reduced hippocampal LTP (van Hasselt et al., 2012) and stress-induced enhancements in cognitive performance (Barha et al., 2007), however the neural basis of these

phenotypes has not been explored in depth. This bias within the literature is typical of neuroendocrine studies of stress reactivity and cognition in general, where these systems are only explored in females when a specific hypothesis related to the influence of reproductive state (*i.e.* pregnancy, lactation) is being explored. In female offspring, the study of the influence of LG on reproduction (*e.g.* sexual and maternal behavior) has focused on hypothalamic regions sensitive to gonadal hormones and targets within the mesolimbic dopamine pathways that have been implicated in the motivation to engage in maternal behavior. The enhanced sexual behavior observed amongst low-LG females is associated with increased estrogen receptor alpha (ER $\alpha$ ) mRNA in the anteroventral paraventricular nucleus of the hypothalamus (AVPN) and increased estrogen sensitivity of these steroid receptors in the AVPN and ventral medial hypothalamus (VMH) (Cameron et al., 2008, 2011). However, these females exhibit reduced estrogen sensitivity within hypothalamic structures that play a functional role in maternal behavior. Female offspring of low- compared to high-LG dams have reduced estrogen-stimulated increases in neuronal activation within the medial preoptic area (MPOA), likely attributable to the reduced levels of ER $\alpha$  in this region (Champagne et al., 2001, 2003). Oxytocin receptor protein levels are reduced in the female offspring of low-LG dams within the MPOA, lateral septum, bed nucleus of the stria terminalis (BNST), PVN, and central nucleus of the amygdala (Champagne and Meaney, 2007;

**Table 2**  
Impact of low vs. high maternal LG on neuroendocrine outcomes in adult female Long-Evans rats.

Brain region	Effect of low vs. high LG	Reference
Lateral septum	↓ oxytocin receptor binding ↓ estrogen-induced oxytocin receptor binding	Champagne et al. (2007) Champagne et al. (2001)
BNST	↓ oxytocin receptor binding	Francis et al. (2002)
MPOA	↓ oxytocin receptor binding ↓ estrogen-induced oxytocin receptor binding ↓ ER $\alpha$ mRNA and protein; ↓ estrogen-induced cFos ↑ <i>Esr1</i> promoter DNA methylation ↓ Stat5b binding to the <i>Esr1</i> promoter ↓ OTR mRNA ↓ ER $\alpha$ -IR ↑ <i>Esr1</i> promoter DNA methylation ↓ H3K4me3 at <i>Esr1</i> promoter ↑ estrogen-induced GnRH-IR	Champagne et al. (2007) Champagne et al. (2001) Champagne et al. (2003) Champagne et al. (2006) Pena et al. (2013) Cameron et al. (2008)
Anteroventral paraventricular nucleus of the hypothalamus	↑ ER $\alpha$ mRNA ↑ estrogen-induced pER $\alpha$	Cameron et al. (2008) Cameron et al. (2008)
Ventromedial hypothalamus (VMH)	↑ pER $\alpha$ -IR (proestrus) ↓ c-Fos-IR (proestrus) ↓ Stat5b binding to the <i>Esr1</i> promoter	Cameron et al. (2011) Cameron et al. (2008)
Hippocampus	↓ EPSPs	van Hasselt et al. (2012)
PVN	↓ oxytocin receptor binding	Champagne et al. (2007)
Amygdala (CN)	↓ oxytocin receptor binding	Francis et al. (2002)
VTA	↓ TH-IR ↓ Lmx1b mRNA; ↓ BDNF mRNA	Pena et al. (2014)

Francis et al., 2002). The mesolimbic dopamine system is also shaped by maternal LG. Adult female offspring of low-LG rat dams have reduced dopaminergic projections from the ventral tegmental area (VTA) and reduced expression of LIM homeobox transcription factor 1 beta (*Lmx1b*) and BDNF in this region (Pena et al., 2014), which suggests a maternal care influence on factors that contribute to dopaminergic cell differentiation and survival in the ventral midbrain.

Exploration of the impact of maternal care on the brain and behavior has typically focused on adult outcomes and illustrate the long-term impact of variation in mother–infant interactions. However, it is increasingly evident that phenotypic consequences of maternal LG emerge during development (see Table 3). In male rat offspring, reductions in hippocampal GR, BDNF, GAD1 and NMDAR subunit expression are apparent by approximately postnatal (PND) 6. At the time of weaning (PND 21), male offspring that have experienced low-LG have continued reductions in hippocampal BDNF and NMDAR subunit expression (Liu et al., 2000; van Hasselt et al., 2012) as well as reduced synaptophysin and NCAM protein levels leading to reduced neuronal survival (Liu et al., 2000; Bredy et al., 2003). Amongst juvenile (PND 40) male offspring of low-LG rat dams, altered serotonin (5-HT) turnover rates are apparent in the PFC, ventral striatum, and hippocampus (Masis-Calvo et al., 2013; Sequeira-Cordero et al., 2013). In female offspring, variation in protein and mRNA levels within the MPOA and VTA associated with maternal LG can be observed as early as PND 6. Female pups that have experienced low-LG, have reduced ER $\alpha$  mRNA and protein levels within the MPOA and decreased dopaminergic projections from the VTA (Pena et al., 2014, 2013; Champagne et al., 2006). At this developmental time point, the expression of cyclin-dependent kinase inhibitor 1C (*cdkn1c*) is reduced, which may alter cell proliferation within the ventral mid-brain of these offspring (Pena et al., 2014). At PND21, female offspring of low-LG rat dams are observed to have reductions in ER $\alpha$  and ER $\beta$  mRNA within the MPOA, reduced *Lmx1b* mRNA within the VTA, and reduced dopamine receptor expression in the nucleus accumbens (Pena et al., 2014, 2013). Amongst juvenile

females, the reduction in MPOA ER $\alpha$  and reduced dopaminergic projections from the VTA associated with low-LG persists (Pena et al., 2014; Pena and Champagne, 2015). The early emergence of these neurobiological effects of maternal care may account for the behavioral phenotypes that also emerge prior to adulthood. Juvenile male offspring of low-LG dams exhibit increased indices of anxiety-like behavior (Masis-Calvo et al., 2013) and low-LG female offspring display decreased maternal sensitivity to donor pups (Pena et al., 2013). Though these developmental studies do provide some insight into the timing of neurobiological change as a consequence of variation in maternal care, a more systematic use of this approach, in which brain-region specific changes in gene expression/protein are assessed at multiple timepoints during development, will be needed to understand the process by which maternal care induces long-term effects. Moreover, our current understanding of what gene targets/systems are affected by maternal LG, developmentally or in adulthood, is based on a priori selection of targets/systems rather than on genome-wide analyses, thus prohibiting conclusions regarding the cascade of changes that occur and the relationship between affected and un-affected target genes. In addition to implementation of un-biased approaches to gene target selection, future studies should also compare and contrast the developmental impact of LG in males and females on the same neuroendocrine/gene targets so as to identify sex differences in response to this critical environmental experience.

## 2.2. Communal rearing

In biparental species, it is evident that offspring development is altered in response to the absence of the father (Ahern and Young, 2009; Cao et al., 2014). In humans, longitudinal studies indicate that early-life transition from a two-biological-parent to single-parent family structure is associated with increased behavioral problems in children (Ryan et al., 2015). However, even in non-biparental species, the benefit of multiple caregivers can be observed. Studies of communal rearing in rodents (primarily mice; *Mus musculus*) indicate that lactating females that are co-housed

**Table 3**  
Developmental impact of low vs. high maternal LG on neuroendocrine outcomes in Long-Evans rats.

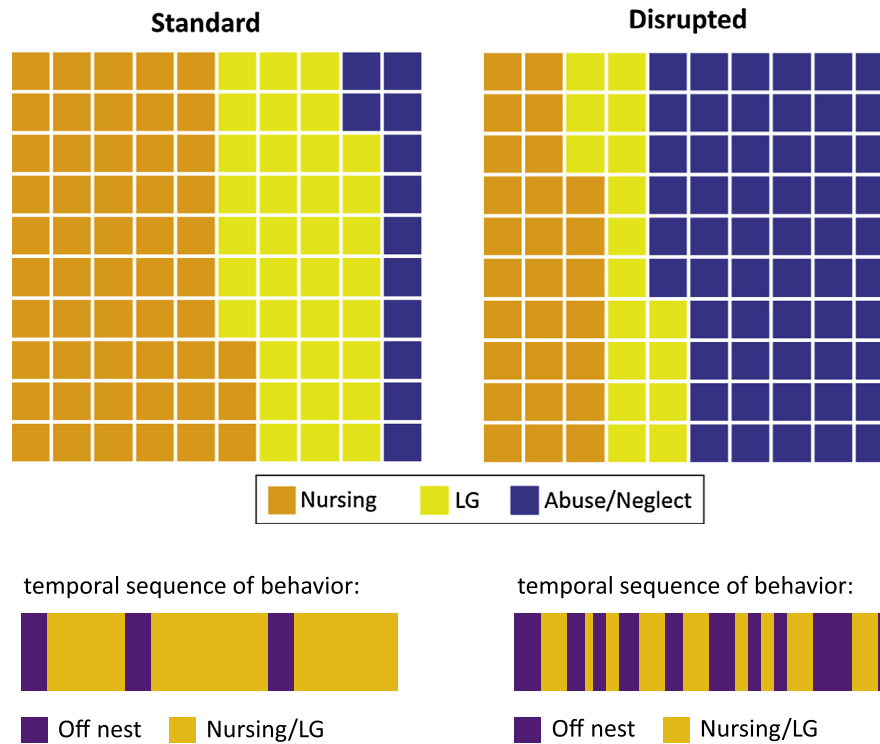
Brain region	Sex	Age	Effect of low vs. high LG	Reference	
PFC	Male	PND 40	↑ 5-HT turnover (ratio of 5HT1A/5-HT)	Masis-Calvo et al. (2013)	
Nucleus accumbens	Female	PND 21	↓ DRD1, ↓ DRD2, ↓ DRD3 mRNA	Pena et al. (2014)	
	Male	PND 40	↓ 5-HT turnover, ↓ TrkB mRNA	Sequeira-Cordero et al. (2013)	
Ventral striatum	Male	PND 40	↑ DOPAC	Masis-Calvo et al. (2013)	
MPOA	Female	PND 6	↓ ER $\alpha$ mRNA ↓ Stat5b protein ↓ ER $\alpha$ -IR	Champagne et al. (2006)	
	Female	PND 21	↓ ER $\alpha$ , ↓ ER $\beta$ mRNA ↑ <i>Esr1</i> promoter DNA methylation ↓ H3K4me3 at <i>Esr1</i> promoter ↑ H3K9me3 at <i>Esr1</i> promoter	Pena et al. (2013) Pena et al. (2013)	
Hippocampus	Female	PND 40	↓ ER $\alpha$ -IR	Pena et al. (2014)	
	Male	PND 4	↓ GAD1 mRNA ↓ NGFI-A, CBP, NAB1, NAB2 and Sp1 protein	Zhang et al. (2010) Hellstrom et al. (2012)	
	Male	PND 6	↑ <i>Nr3c1</i> DNA methylation ↓ GR mRNA and protein ↓ CBP, H3K9Ac and NGFI-A binding to the <i>Nr3c1</i> promoter ↓ MBD2 mRNA	Weaver et al. (2004) Weaver et al. (2007) Weaver et al. (2014)	
	Male	PND 8	↓ BDNF mRNA ↓ NR2A, ↓ NR2B NMDAR subunit mRNA	Liu et al. (2000)	
	Male	PND 21	↓ neuronal survival ↑ apoptosis; ↓ bFGF ↑ <i>Nr3c1</i> DNA methylation ↓ BDNF mRNA (exon IX)	Bredy et al. (2003) Weaver et al. (2004) van Hasselt et al. (2012)	
	Male	PND 18	↓ synaptophysin, ↓ NCAM protein ↓ NR2A, ↓ NR2B NMDAR subunit mRNA	Liu et al. (2000)	
	Male	PND 40	↓ 5-HT turnover	Sequeira-Cordero et al. (2013)	
	VTA	Female	PND 6	↓ TH-IR ↓ <i>cdkn1c</i> mRNA	Pena et al. (2014)
		Female	PND 21	↓ <i>Lmx1b</i> mRNA	Pena et al. (2014)
		Female	PND 40	↓ TH-IR	Pena et al. (2014)

can form a communal nest, whereby multiple lactating females engage in care toward a pooled group of offspring. This rearing experience has been demonstrated to increase maternal behavior (LG and nursing) of individual dams and to enhance growth rates of offspring relative to standard laboratory rearing (a single mouse dam rearing a single litter) (Curley et al., 2009; Sayler and Salmon, 1969; Branchi et al., 2006). Though the adaptive benefit of this rearing strategy for mothers likely depends on the degree of relatedness of the females participating in the communal care of the litters (Konig, 1993), from the perspective of the offspring, communal rearing can be viewed as an effective approach for enhancing both mother–infant and peer interactions (Branchi et al., 2013). However, similar to the case of natural variations in LG, the developmental impact of being reared in a communal nest may be modulated by the amount of care received by the individual pup. This within-nest phenomenon is particularly evident when nests are composed of pups of varying ages, where the youngest and oldest pups in the nest have been observed to receive relatively higher levels of maternal care compared to other age groups (Branchi et al., 2009).

Communal rearing in mice has been found to be associated with reductions in anxiety-like and depressive-like behavior as well as increases in social interactions and increased social competence in adult male mouse offspring (Branchi et al., 2006, 2006; D'Andrea et al., 2007). Communal rearing also alters responsiveness to antidepressants (Branchi et al., 2009) and may buffer adult male offspring from the effects of social stress (Branchi et al., 2013). Within the brain, communal rearing is associated with increased BDNF protein levels within the hippocampus, hypothalamus, and striatum, increased nerve growth factor (NGF) protein levels in the hippocampus and hypothalamus (Branchi et al., 2006) and decreased hippocampal 5-HT levels (Connors et al., 2015). These increased neurotrophin levels are similar to the

developmental effects of high-LG and may account for the increased cell survival observed within the hippocampus (Branchi et al., 2006). Oxytocin receptor levels are elevated within the anterior cortical nucleus of the amygdala (ACo), central amygdala (CeA), and dorsal posterior medial amygdala (dpMA) of communal vs. standard reared males, though this effect may be attributable to increased peer social interactions, rather than increased maternal care (Branchi et al., 2013). Though studies of the neurobiological and behavioral impact of communal rearing in mice have focused primarily on male offspring, comparison of the behavioral impact of communal vs. standard rearing on males and females suggests that this early social experience may influence depressive-like behavior more significantly in females and that males and females do show a differential response to postnatal rearing in a communal nest (D'Andrea et al., 2010).

Variation in LG and the experience of communal rearing has been observed to induce multigenerational effects via alterations in the maternal behavior of female offspring. In Long-Evans rats, offspring of low-LG dams display increased LG in adulthood and this phenotype has also been observed in the grand-offspring generation (Francis et al., 1999; Champagne et al., 2003). Similarly, female mouse offspring (Balb/c) that have been reared in a communal nest exhibit elevated maternal care toward their own offspring, with increases in both nursing and LG observed in these females when rearing their offspring under non-communal conditions (Curley et al., 2009). These females also have reductions in anxiety-like behavior. Within the next generation (i.e. daughters of communally reared female mice), there are also indices of enhanced maternal behavior and enhanced growth of offspring (Curley et al., 2009). Multigenerational effects on maternal behavior as a consequence of variation in LG in rats have been associated with variation in hypothalamic neuropeptide receptor levels (Champagne and Meaney, 2007), and these systems may also be



**Fig. 1.** Comparison of maternal care in rats under standard rearing conditions or following disruption. Removal of nesting materials from the home-cage is disruptive to maternal behavior at the level of frequency and pattern of care. Waffle chart indicating percentage of time spent in each behavior (one block = 1%). Frequency of abusive mother–infant interactions is increased following disruption and frequency of nurturing care (nursing and LG) is decreased following disruption. In addition, the pattern of behavior is altered. Home-cage disruptions lead to more fragmented bouts of maternal care due to frequent time not in contact with pups.

involved in the transmission of the effects of communal rearing in mice. At PND 28 (weaning), female Balb/c mice that have experienced communal vs. standard rearing during their postnatal development have elevated oxytocin receptor protein levels in the lateral septum, endopiriform nucleus, agranular insular cortex, and BNST and reduced vasopressin 1a receptor (V1a) protein levels in the lateral septum. Among the daughters of these females (who have not been exposed directly to communal rearing), the increased levels of oxytocin receptors and decreased V1a receptors in the lateral septum persists and is observed in adulthood (Curley et al., 2009). It is presumed that this maternal transmission of the impact of communal rearing is mediated by the variation in maternal care induced by this manipulation (though this has yet to be established *via* cross-fostering/cross-rearing manipulations), suggesting strong parallels between these two approaches in the study of the neurobiological impact of maternal care.

### 2.3. Home-cage disruption

Though approaches to the study of the impact of maternal care on offspring development that involve variation in LG or communal rearing have typically focused on the quantity of maternal care as a critical feature, the quality of those interactions may also vary in these models and serve as a significant predictor of developmental outcomes. For example, Long-Evans rat dams that engage in high-LG display long continuous bouts of maternal care whereas low-LG dams engage in short bursts of maternal care that are juxtaposed with time off the nest (Pena et al., 2013). This fragmentation of care can also be induced in laboratory rodents through disruption to the availability of nesting material in the home-cage (see Fig. 1). Limiting the quantity of bedding material available to lactating rat dams results in reduced levels of nursing and LG and increases the amount of time pups are out of the nest and not in contact with dams (Brunson et al., 2005; Ivy et al., 2008).

The shorter duration of bouts of maternal care observed results in an overall impact on the sequence of behavior – with the limited bedding condition inducing a more fragmented behavioral pattern (Ivy et al., 2008). Following a week of housing under limited bedding conditions, rat dams exhibit increased adrenal weights, increased basal plasma corticosterone levels, and decreased CRH mRNA within the PVN, suggesting that this manipulation serves as a chronic stressor (Ivy et al., 2008). However, if dams are returned to a standard rearing environment with appropriate levels of bedding after a week of limited-bedding exposure, maternal behavior toward pups is normalized. Thus, this approach can determine the impact of altered maternal care during a specific window during development. This manipulation can also increase the frequency of abusive maternal behavior (stepping on or roughly handling pups; see Fig. 1) (Raineke et al., 2010) which may also contribute to the developmental outcomes observed in offspring. This methodological approach may model the parental stress and disrupted parent–offspring interactions that are observed in humans and non-human primates under conditions of low or variable resource availability (*i.e.* low socioeconomic status; variable foraging demand) which have been associated with elevated CRF levels and increased behavioral problems in childhood (Coplan et al., 2005; Rijlaarsdam et al., 2013).

Immediately following a week of exposure (PND 2 to PND 9) to fragmented care within the limited nesting materials rearing approach, there are neuroendocrine changes induced suggestive that pups have experienced chronic stress. At PND 9 (immediately following disrupted maternal care), rat pups have increased adrenal weights, decreased body weights, and increased basal plasma levels of corticosterone (Avishai-Eliner et al., 2001; Gilles et al., 1996). The mRNA levels of several target genes that regulate stress reactivity are altered by the experience of fragmented maternal care, including reduced CRF mRNA within the PVN, reduced hippocampal CRF<sub>1</sub> receptor mRNA, and reduced GR mRNA within

the PVN and frontal cortex (Avishai-Eliner et al., 2001). Structural and molecular changes within the hippocampus suggest that fragmented maternal care also induces reduced synaptic plasticity. Mouse pups (C57BL/6) reared under conditions of reduced nesting material have reduced dendritic length and arborization in CA3 pyramidal neurons. In addition, these pups have reduced hippocampal protein levels of synaptophysin, post-synaptic protein PSD-95, nectin-3, and NMDA receptor subunit expression (NR1, NR2A) (Liao et al., 2014). Exposure to this disruption in care also alters the response of rat pups to the mother and increases amygdala activation in response to maternal odors (Rainekei et al., 2010). These altered behavioral and neural responses are suggestive of impairments in social attachment to the mother which may persist even when maternal behavior is normalized after PND 9.

The long-term effects of home cage disruption that persist to weaning and into adulthood, suggest that neural systems regulating response to stress and neural plasticity are particularly sensitive to the impact of this postnatal manipulation (see Chen and Baram, *in press* for review). In mice, increased anxiety-like behavior in response to fragmented maternal care is evident in adulthood as are deficits in learning/memory (Wang et al., 2012, 2011). Within the adult brain, altered CRH mRNA within the PVN in mice (Rice et al., 2008) and reduced BDNF mRNA within the prefrontal cortex in rats (Roth et al., 2009) are associated with the postnatal experience of disrupted maternal care. However, temporal analyses indicate that the structural changes in the brain that may account for the behavioral phenotypes observed in this model may vary in expression from middle age to old age. For example, in middle age rats (4–5 months), reduced hippocampal dendritic complexity and length have been observed in offspring that have experienced disrupted maternal care (Brunson et al., 2005). However, indices of LTP have been observed to be impaired in old age (12 months) but not middle age offspring (Brunson et al., 2005). These findings suggest dynamic variation in the brain that is triggered by postnatal events but may express itself differently at a cellular and molecular level dependent on age.

Similar to approaches examining variation in frequency of LG and communal rearing, disruption to the home-cage environment has not typically examined the differential impact of this rearing environment on males vs. females. Many studies examining the immediate impact of this rearing experience on PND 9 pups have included both males and females but have not examined outcomes in these groups separately. In cases where this analysis has been conducted, it is evident that though there is significant overlap in the impact of disrupted maternal care on brain gene expression in males and females, there are also synaptic structural differences between males and females in response to this postnatal experience (Liao et al., 2014). In adulthood, most outcomes have been studied exclusively in males. However, similar to the LG and communal rearing approaches, adult females do manifest changes in reproductive behavior. Lactating female rats that have experienced increased fragmented care during their postnatal development engage in a higher frequency of abusive care toward their own pups (Roth et al., 2009). Consequently, the effects of disrupted maternal care may persist across generations via the transmission of abusive maternal care, though the mechanism of this transmission needs to be more thoroughly investigated, and may also involve prenatal factors (Roth et al., 2009).

### 3. Mechanistic pathways linking maternal care to offspring outcomes

Variation in maternal care, whether it is occurring naturally or achieved through manipulation of the rearing environment, acts as a sensory signal to offspring with immediate consequences that

shape developing neural systems. Both olfactory and tactile signals from the mother impact the developing brain. Neural activation is stimulated by odors associated with the early rearing environment, which may facilitate social learning (Sullivan et al., 1990). This neural response to maternal odors is enhanced when combined with licking-like tactile stimulation (Sullivan and Leon, 1986), suggestive that both the presence of the mother and the care provided by the mother induce alterations in brain function. The somatosensory stimulation provided by licking has been demonstrated to increase serum lactate in the brain of newborn but not week-old rat pups (Alasmi et al., 1997). Tactile stimulation in maternally separated PND 8–10 rat pups leads to increased brain levels of ornithine decarboxylase and growth hormone and decreased serum corticosterone, indicating that this stimulation can attenuate the effects of maternal separation (Pauk et al., 1986). These effects can also be observed at the level of gene expression, with licking-like tactile stimulation preventing maternal separation induced decreases in hippocampal GR mRNA and CRF mRNA in the PVN (van Oers et al., 1998) and attenuating the effects of complete maternal deprivation (Lovic and Fleming, 2004). In humans, preterm infants also show enhanced growth and neurodevelopment in response to postnatal tactile stimulation (Field et al., 1986) and physical touch from mothers can attenuate infant stress responses (Feldman et al., 2010). Overall, there is significant support for the hypothesis that tactile stimulation received by offspring during mother–infant interactions can influence neural and physiological systems. However, given the diverse effects of maternal care on both short- and long-term developmental outcomes, it will be important to further explore how general signals (e.g. increased growth factors, energy availability, glucocorticoids) integrate with multiple neural systems to achieve specific cellular and molecular outcomes.

A mechanistic question that has been increasingly explored in the context of the impact of maternal care on brain development has focused on the changes in gene expression that are evident even in adulthood (see Tables 1 and 2). The regulation of gene expression is a dynamic process, involving coordinated signals from hormones, cellular signaling pathways, and transcription factors. In the case of the long-term effects of variation in maternal care on gene expression, it is evident that a “cellular memory” of the events of postnatal development is predicting levels of mRNA within the brain. The stability of these effects suggests the role of epigenetic mechanisms. DNA methylation, post-translational histone modifications, and small non-coding RNAs are epigenetic molecular processes that alter gene expression without alteration to DNA sequence (see Jenuwein and Allis, 2001; Razin, 1998; Sato et al., 2011 for review). DNA methylation is generally considered the most stable of these processes, due to the strong covalent bond that chemically links the methyl-group to cytosines within the DNA (Razin, 1998). Though it had been assumed that epigenetic alterations had limited plasticity beyond the early stages of embryonic development, there is increasing evidence that these processes are highly dynamic throughout the lifespan in response to a variety of environmental signals. In particular, variation in the quality and/or quantity of maternal care is associated with epigenetic variation in the brain of offspring.

#### 3.1. Epigenetic influence of maternal LG on the *Nr3c1* gene

Hippocampal levels of GR serve a critical negative-feedback role within the HPA response to stress (Sapolsky et al., 1985) and reduced levels of hippocampal GR among the male offspring of low-LG rat dams has been hypothesized to account for the heightened plasma corticosterone response to stress in these offspring (Liu et al., 1997). Levels of hippocampal GR protein and mRNA are decreased in PND 6 male offspring that have

experienced low levels of postnatal LG and this effect persists into adulthood (Weaver et al., 2004, 2007; Liu et al., 1997). Analysis of DNA methylation within the promoter region of the *Nr3c1* gene, which encodes for GR, indicates that by PND 6 there is increased DNA methylation of *Nr3c1* in offspring of low- compared to high-LG rat dams (Weaver et al., 2004). Group differences in DNA methylation are not observed prior to PND 6 and then remain constant at PND 21 and in adulthood (PND 90). This differential DNA methylation is particularly evident at the NGFI-A binding site proximal to the *Nr3c1* transcription start site. NGFI-A [nerve growth factor-induced protein A; also known as EGR-1 (early growth response protein 1) or Zif268 (zinc finger protein 268)] is a transcription factor (Knapska and Kaczmarek, 2004). Low levels of maternal care are associated with decreased NGFI-A protein levels at PND 4 and reduced binding of NGFI-A to the *Nr3c1* gene promoter at PND 6 (Weaver et al., 2004, 2007; Hellstrom et al., 2012). These protein–DNA interactions may be downstream of thyroid hormone signaling that is induced acutely following LG. Plasma levels of triiodothyronine (T3) are increased immediately following mother–infant interactions in high-LG litters and the T3 precursor, thyroxine (T4), is elevated in the plasma of low-LG offspring (Hellstrom et al., 2012). This thyroid signaling is necessary for NGFI-A binding to the *Nr3c1* gene promoter and is facilitated by 5-HT receptor activation. Provision of licking-like tactile stimulation can trigger these pathways resulting in dynamic epigenetic changes (Hellstrom et al., 2012). Levels of methyl-CpG binding domain proteins (MBDs), particularly MBD2, may facilitate these epigenetic effects as MBD2 mRNA levels are increased in PND 6 offspring of high-LG dams in the CA1 and dentate gyrus and levels of MBD2 expression are correlated with levels of GR expression (Weaver et al., 2014).

Though epigenetic regulation of *Nr3c1* in the hippocampus in response to maternal LG in rats has been studied in depth, it is important to note that other gene targets within the hippocampus are also altered in expression in response to low- vs. high-LG. In the adult male hippocampus, variation in maternal LG is associated with differential expression of over 900 genes (Weaver et al., 2006). Analyses of DNA methylation and histone modifications within chromosome 18 (which contains the *Nr3c1* gene) indicates multiple loci at which there are increases or decreases in DNA methylation and histone acetylation (H3K9Ac) (McGowan et al., 2011). Target gene analyses indicate elevated DNA methylation and reduced histone acetylation within the *Gad1* (encoding glutamate decarboxylase 1) and *Grm1* (encoding metabotropic glutamate receptor 1) gene promoters (Zhang et al., 2010; Bagot et al., 2012). The broad epigenetic changes in the hippocampus in response to maternal LG may be due to alterations in genes that contribute generally to epigenetic regulation, such as MBDs and DNA methyltransferases, which have been shown to be altered in expression when comparing offspring of low- vs. high-LG dams (Zhang et al., 2010; Weaver et al., 2014). Though these changes emerge during the first week postnatal, it is evident that epigenetic plasticity is present in the adult brain, and pharmacological targeting of methylated CpGs or histones in adulthood can result in the reversibility of the epigenetic effects of postnatal LG (Weaver et al., 2004, 2005).

### 3.2. Epigenetic influence of maternal LG on the *Esr1* gene

Sensitivity to hormones is a key determinant of postpartum maternal behavior in rodents, particularly the elevated estrogen levels that coincide with late pregnancy (see Rosenblatt et al., 1988 for review). The genomic effects of estrogen are mediated through interactions with nuclear estrogen receptors, primarily estrogen receptor alpha (ER $\alpha$ ; encoded by the *Esr1* gene) and estrogen receptor beta (ER $\beta$ ; encoded by the *Esr2* gene) (McEwen, 2001).

Thus, the reduced levels of hypothalamic ER $\alpha$  observed in the female offspring of low-LG rat dams acts to reduce estrogen sensitivity and may contribute to the reduced levels of maternal behavior observed in these offspring. Importantly, the reduced levels of ER $\alpha$  mRNA and protein are present in the developing brain, emerging at PND 6 (Pena et al., 2013; Champagne et al., 2006), prior to the hormonal activation of reproductive systems. Analyses of the levels of the transcription factor Stat5b (signal transducer and activator of transcription 5B) indicate that female offspring of high-LG dams have elevated hypothalamic Stat5b protein at PND 6 (Champagne et al., 2006). These elevations in Stat5b may promote increased transcriptional activity and reduce the likelihood of epigenetic gene silencing of *Esr1*. By PND 21, female offspring reared by high-LG dams have decreased DNA methylation within the promoter region of the *Esr1* gene in comparison to offspring of low-LG dams (Pena et al., 2013). Histone marks at the *Esr1* gene promoter are also altered in association with LG, with histone trimethylation at lysine 4 (H3K4me<sup>3</sup>) increased and histone trimethylation at lysine 9 (H3K4me<sup>3</sup>) decreased in the hypothalamus of offspring reared by high-LG rat dams (Pena et al., 2013). Collectively, these epigenetic marks contribute to a more accessible/active chromatin state in offspring of high-LG dams and transcriptional repression of *Esr1* in the MPOA of offspring of low-LG dams.

Epigenetic regulation of *Esr1* within the brain has been observed in response to prenatal exposure to endocrine disruptors (Kundakovic et al., 2013) and may be modulated by hormonal exposure during development to generate sexual dimorphism in hypothalamic ER $\alpha$  levels (Nugent et al., 2015). Adult female rats express higher levels of ER $\alpha$  within the MPOA compared to male rats and this sex differences is associated with increased *Esr1* gene promoter DNA methylation in males (Kurian et al., 2010). If females are provided with high levels licking-like tactile stimulation from PND 5–7, sex differences in *Esr1* gene promoter DNA methylation are ablated due to increased *Esr1* gene promoter DNA methylation in females. Thus, tactile stimulation comparable to that received via mother–infant interactions can alter the epigenetic state of *Esr1*. This effect of tactile stimulation on *Esr1* is not specific to the MPOA and can also be observed in the developing amygdala (Edelmann and Auger, 2011). Though *Esr1* has been a primary focus of epigenetic studies of the impact of maternal care in females, it is unlikely that maternal influences are specific to this gene target. At PND 21, female offspring of high-LG dams also display increased ER $\beta$  mRNA levels within the MPOA (Pena et al., 2013) and increased expression of dopamine receptors within the nucleus accumbens (Pena et al., 2014), suggestive of broader epigenetic consequences of maternal care.

### 3.3. Epigenetic influence of communal rearing on the *Bdnf* gene

Neural plasticity is a critical feature of brain development and function, and underlies the ability to adapt to novel environments and experiences. The neurotrophin BDNF has been implicated in the process of neural plasticity (see Cowansage et al., 2010 for review) and it is also evident that variation in maternal care can alter levels of BDNF in the brain. Among adult male offspring that have experienced communal rearing, there are increases in hippocampal BDNF (Branchi et al., 2006). Genetic and epigenetic analyses of the BDNF promoter reveal the complexity of this gene, which contains multiple promoter regions which are responsive to promoter-specific transcription factors and which generate tissue-specific transcripts (Aid et al., 2007). These gene promoters also differ in their transcriptional response to epigenetic variation, indicated by pharmacological studies which induce decreased DNA methylation or increased histone acetylation (Aid et al., 2007). Within the hippocampus of adult male mice that have experienced communal rearing, increased histone acetylation is associated with



several *Bdnf* promoters, including promoter I, IV, and VII, suggesting a more transcriptionally active state (Branchi et al., 2011). This epigenetic variation may account for the increased plasticity of BDNF levels in communally reared offspring in response to novelty. Though DNA methylation has not been explored in this paradigm, it seems likely that promoter specific variation in this epigenetic mark may also be associated with communal rearing and contribute to resulting changes in BDNF mRNA and protein levels in adulthood.

#### 3.4. Epigenetic influence of fragmented and abusive care on the *Bdnf* gene

Neural plasticity may also be impacted by disruption to the home-cage environment during the postnatal period and epigenetic analyses of the *Bdnf* gene suggest that while communal care promotes a more accessible chromatin state within the *Bdnf* gene, the converse is true in response to fragmented/abusive care. Exposure to fragmented/abusive care induced through limited nesting material is associated with increased DNA methylation within *Bdnf* promoter IX in the prefrontal cortex in rats at PND 8 and PND 30 (Roth et al., 2009). In adulthood, this increased DNA methylation is observed in *Bdnf* promoters IV and IX in the prefrontal cortex and administration of zebularine, a drug that inhibits DNA methylation, can alter this epigenetic effect (Roth et al., 2009). These epigenetic effects vary as a function of both sex, age, and the brain region being analyzed. At PND 30, abuse-exposed male rats have elevated *Bdnf* promoter IV DNA methylation in the prefrontal cortex whereas in females there is decreased DNA methylation in this genomic region. In adulthood, both males and females are observed to have increased DNA methylation in *Bdnf* promoter I in the prefrontal cortex, but at promoter IV only abuse-exposed females are observed to have increased DNA methylation (Blaze et al., 2013). At PND 8, abuse-exposed females have increased DNA methylation of *Bdnf* promoter IV in the ventral hippocampus (Roth et al., 2014). Within the amygdala, abuse-exposure is associated with decreased BDNF promoter I DNA methylation in females and decreased *Bdnf* promoter IV DNA methylation in males. However, in adulthood the direction of effect of abusive care on *Bdnf* DNA methylation in the hippocampus and amygdala suggests dynamic epigenetic changes occurring across the lifespan (Roth et al., 2014). This phenomenon is consistent with observed biphasic responses in studies of early life adversity and expression of the *Bdnf* gene (Suri et al., 2013).

Though BDNF has been the focus of much of the epigenetic analyses of the impact of abusive/fragmented care, the molecular changes within the *Bdnf* gene are likely part of broader epigenetic variation induced by this early life experience. Within the dorsal hippocampus, PND 30 male rat offspring that have experienced abusive care have increased global levels of DNA methylation whereas abuse-exposed female offspring have reduced global levels of DNA methylation within the ventral hippocampus (Doherty et al., 2015). Genes associated with epigenetic remodeling are also altered in expression in response to abusive care. At PND 30, there is decreased expression of the methyl-binding protein MeCP2 within the prefrontal cortex of abuse-exposed males (Blaze and Roth, 2013). In adulthood, expression of the DNA methyltransferases DNMT1 (in males) and DNMT3a (in males and females) in the prefrontal cortex are decreased by abuse-exposure. The decreased expression of MeCP2 in males is maintained in adulthood and decreased expression of *Gadd45b* (growth arrest and DNA-damage-inducible beta), a gene involved in activity-dependent reductions in DNA methylation, is observed in the prefrontal cortex of both males and females (Blaze and Roth, 2013). Reduced expression of the histone deacetylase 1 gene (*Hdac1*) is also observed in the prefrontal cortex of abuse-exposed adult male offspring, suggesting that post-translational histone modification

may also account for the long-term impact of disruptions to mother–infant interactions.

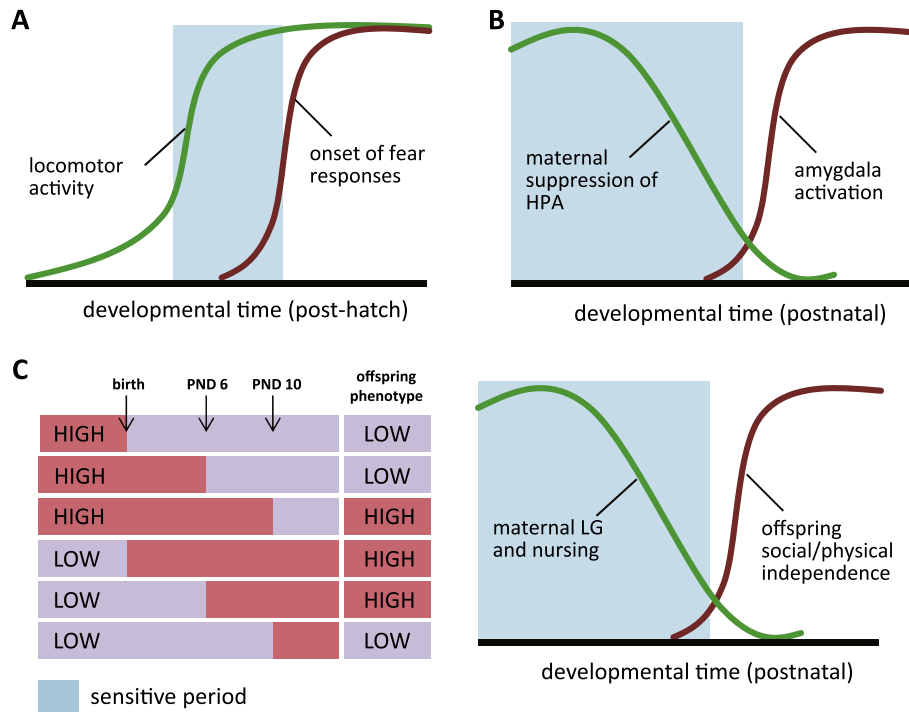
#### 4. Timing and sensitive periods

Though the postnatal period of development can be thought of generally as a sensitive period, a critical question within the context of studies of mother–infant interactions is regarding the temporal dynamics of the sensitivity to maternal care. Studies of variation in LG focus on the impact of high- vs. low-LG during the first week of life. This timing is when these dams are maximally divergent in their maternal care as LG and nursing decline in general frequency progressively throughout the postnatal period (Jensen Pena and Champagne, 2013). The importance of this time period are also highlighted by findings that neonatal handling in rats, a manipulation that enhances LG, is only effective in altering developmental outcomes if conducted during the first two weeks postnatal (Meaney and Aitken, 1985). The timing of the effects of communal rearing are more difficult to discern as this rearing environment encompasses the entire postnatal period. In the case of the disruption to the home-cage environment, this manipulation is typically conducted during the first week postnatal, ending on PND 8–9. This manipulation, similar to maternal separation, offers a paradigm that allows for varying timing and duration of exposure – though the analyses of these variables have yet to be explored. Here we will explore how timing/sensitive periods has been explored within the context of social interactions occurring during development and how these studies contribute to our understanding of the temporal dynamics and mechanisms of response to maternal care.

##### 4.1. Sensitive periods for behavioral imprinting

Behavioral imprinting, a phenomenon where newborn chicks form a long-term “attachment” to their parents following hatching, has been a classic model for exploring sensitive/critical periods for social learning (see Fig. 2A). These studies have clearly identified a developmental window, during which time, exposure to the imprinting stimulus (typically the parent but can include any visual/auditory stimuli) is necessary to ensure behavioral imprinting. Within the lab, studies of behavioral imprinting involve post-hatching exposure to a stimulus (e.g. replica duck, geometric shape, color) followed by assessment of the amount of ambulatory behavior the chick will engage in to follow the stimulus upon re-exposure. In ducklings, exposure to the imprinting stimulus 16–17 h post-hatch is maximally effective in generating a positive response (i.e. increased ambulatory behavior toward that stimulus), whereas exposure after 48 h post-hatch generates minimal levels of imprinting (Hess, 1958). It has been speculated, that the factors contributing to this temporally specific window of plasticity include the ability to engage in locomotor activity and the onset of fear responses (Hess, 1959). Speed of locomotor activity in chicks reaches a peak 16–17 h post-hatch and then plateaus. Thus, the ability to demonstrate imprinting will be limited until maximal ambulatory behavior can be achieved. Prior to post-hatch day 12, chicks do not engage in fear responses to the imprinting stimulus. However, after post-hatch day 17, an increasing percentage of chicks emit distress vocalizations when presented with the imprinting stimulus (Hess, 1959), thus promoting avoidance rather than approach behaviors. Interestingly, the quality of the social environment can alter the temporal dynamics of imprinting, with increased social contact prolonging the time period when imprinting is possible (Canon, 1959).

The neural mechanisms involved in shaping the sensitive period for behavioral imprinting likely involve cellular/molecular changes that contribute to synaptic plasticity. Imprinting stimulates NMDA



**Fig. 2.** Sensitive periods in the context of mother–infant interactions. (A) Behavioral imprinting studies have identified a sensitive period (blue shaded area) for imprinting during post-hatch development. This sensitive period is generated through increasing locomotor behavior of chicks which peaks at the start of the sensitive period. The end of the sensitive period is driven by the development of fear responses to the imprinting stimuli. (B) Shock–odor conditioning in rat pups has identified a sensitive period for odor conditioning that starts to decline at PND 10. During this sensitive period, HPA responses and amygdala activation are attenuated. (C) Cross-fostering between low and high LG dams indicates a sensitive period for maternal LG. Cross-fostering at birth or PND 6 is effective at shifting offspring phenotype toward that predicted by the foster dam. However, cross-fostering at PND 10 does not shift offspring phenotype. This sensitive period is likely mediated by the high levels of maternal care occurring during the first week postpartum, the heightened group differences in maternal LG during this time, and the increasing physical and social independence from the dam that occurs after this time.

receptors (McCabe and Horn, 1988) and pharmacological antagonism of these receptors can block the formation of imprinting (McCabe et al., 1992). Expression of the NR2B subunit of the NMDA receptor may create the windows of plasticity to imprinting. Expression levels of the NR2B subunit is elevated in the hyperpallium densocellulare post-hatch but then replaced by NR2A subunits at later developmental time points (Nakamori et al., 2010) and may account for reduced sensitivity to social learning. However, when NMDA receptors are pharmacologically blocked within the sensitive period and chicks are dark-reared (preventing imprinting opportunities), the sensitive period for imprinting can be extended to 8 days post-hatch (Nakamori et al., 2010). Extension of the sensitive period can also be achieved through manipulation of the thyroid hormone system. Thyroid hormones peak at the time of hatching and inhibiting thyroid signaling can prevent imprinting (Yamaguchi et al., 2012). Moreover, increasing T3 levels during the sensitive period can extend the sensitive period and increasing T3 levels beyond the sensitive period can re-open a period of sensitivity for behavioral imprinting (Yamaguchi et al., 2012). Thyroid hormone levels can impact NMDA receptor function and subunit expression and so these hormonal signals likely interact with NMDA-mediated synaptic plasticity to shape the sensitive period to this early life experience (Lee et al., 2003). Collectively, these neural and behavioral changes promote approach behaviors toward parents in developing offspring in the early phases of development.

#### 4.2. Timing of infant attachment

Though behavioral imprinting can be achieved through use of abstract stimuli, this phenomenon is thought to serve primarily as a mechanism to achieve parent–infant attachment. In laboratory rodents, this phenomenon can also be established by examining

olfactory conditioning in neonatal rat pups (see Fig. 2B). Pairing a shock exposure with an odor can promote approach responses to the odor from birth to until PND 10 (Sullivan et al., 2000). This approach learning is facilitated by an immature fear response system and low shock-induced plasma corticosterone levels characteristic of the stress hyporesponsive period (Sapolsky and Meaney, 1986). From PND 10 onward, shock–odor pairings promote odor avoidance behaviors. Thus, there is a sensitive period for approach learning which may contribute to the formation of an attachment relationship. During the sensitive period, amygdala activation is suppressed during conditioning whereas avoidance responses occur in later development when amygdala activation is heightened during conditioning (Sullivan et al., 2000). Levels of plasma corticosterone are also a critical modulator of this sensitive period. During the first two weeks postnatal, rat pups have an attenuated HPA response to stress (Sapolsky and Meaney, 1986). This hyporesponsivity is associated with a period of high-levels of mother–infant interactions and absence of the mother during this period, through maternal separation, results in a robust elevation in plasma corticosterone levels in response to stress (Cirulli et al., 1994). Within the postnatal period, elevations in corticosterone at PND 6 (but not PND 5) can switch odor–shock conditioning to avoidance responses (Upton and Sullivan, 2010). However, a premature switch occurring during the sensitive period does not appear to permanently close the sensitive period, indicated by the ability to induce approach behavior when a new odor is presented during subsequent conditioning trials (Upton and Sullivan, 2010). Inhibition of corticosterone, either pharmacologically or through presence of the mother can extend the sensitive period for approach learning at PND 15 (Upton and Sullivan, 2010). However, this appears to be the furthest time point in which approach rather than avoidance responses can be achieved through

odor-shock pairings. The presence of the mother during post-sensitive period odor-shock conditioning inhibits amygdala activation and this effect is mediated through maternal suppression of pup corticosterone release (Moriceau and Sullivan, 2006). These neuroendocrine characteristics of the neonatal rat pup may account for the approach behaviors observed in offspring exposed to abusive caregiving. Within the home-cage disruption paradigm, it has been noted that pups exposed to an abusive dam will continue to seek mother–infant interactions with the dam, despite the adversity associated with those interactions (Roth and Sullivan, 2005).

#### 4.3. Impact of cross-fostering

The impact of postnatal maternal care on development can be most clearly illustrated in cross-fostering or adoption studies. In humans, the impact of postnatal social deprivation in the form of institutional rearing has been found to more severely impact cognitive ability if individuals are adopted into families after six months of institutionalization (Beckett et al., 2006) – suggesting that the duration of maternal absence is predictive of long-term outcomes. Intervention studies, in which institutional reared infants are fostered into a caregiving family, indicate that the HPA response to stress can be altered by altering the quality of the caregiving environment. Moreover, there appears to be a sensitive period for these effects, with intervention effects only evident if fostering is conducted prior to two years of age (McLaughlin et al., 2015). Cross-fostering studies in non-human primates indicate that the transmission of abusive caregiving behavior is related to the abusive phenotype of the rearing rather than the biological mother (Maestripieri, 2005). In rodents, cross-fostering at birth between phenotypically divergent individuals can result in a shift in phenotype in the direction of the foster/rearing mother, suggesting the impact of maternal care. For example, among rats selectively bred for emotionality (response to novelty), which generates high responders (HR; e.g. highly exploratory and impulsive) vs. low responders (LR; e.g. heightened anxiety- and depressive-like behavior), cross-fostering at birth between HR and LR results in reduced anxiety-like behavior and altered gene expression in the amygdala of LR offspring reared by HR dams (Cohen et al., 2015). In mice selectively bred for alcohol preference [high alcohol preference (HAP) vs. low alcohol preference (LAP)], cross-fostering at birth indicates that HAP pups reared by LAP dams have reduced levels of alcohol preference. However, an effect of cross-fostering on alcohol preference is not observed in LAP pups reared by HAP dams, indicating some constraints on this maternal influence (Barrenha and Chester, 2012). Balb/c and C57BL/6 (B6) mice differ on multiple neurobiological and behavioral measures, including anxiety-like behavior (Thompson, 1953), which is elevated in Balb/c mice, and maternal behavior, with Balb/c lactating females exhibiting comparatively less maternal LG toward pups (Champagne et al., 2007). Use of both prenatal (embryo transfer) and postnatal cross-fostering indicates that the phenotype of a B6 mouse can be shifted toward the phenotype of a Balb/c mouse on anxiety-like measures if the B6 embryo and developing pup are exposed to the Balb/c maternal environment (Francis et al., 2003). In this case, postnatal cross-fostering alone was not sufficient to shift phenotype, indicating the influence of the prenatal period.

Exploration of the impact of natural variations in maternal behavior has used postnatal cross-fostering to illustrate the link between the experience of LG and the long-term consequences of LG observed in adulthood (see Tables 1 and 2). The LG status (low vs. high) of a dam is highly stable across subsequent litters allowing for a characterization of this phenotype prior to initiating cross-fostering (Champagne et al., 2003). Cross-fostering pups on

the day of birth between low- and high-LG dams reveals that it is the rearing mother rather than the biological mother LG status that is predictive of exploratory behavior, GR expression, and *Nr3c1* DNA methylation in adult male rat offspring (Weaver et al., 2004; Francis et al., 1999). Thus, offspring born to a low-LG dam and cross-fostered at birth to a high-LG dam display phenotypes associated with high-LG. The converse is evident in offspring born to a high-LG dam and cross-fostered at birth to a low-LG dam. In the case of female offspring, levels of ER $\alpha$  mRNA in the MPOA and maternal LG displayed in adulthood are also predicted by the status of the rearing mother when cross-fostering is conducted on the day of birth (Champagne et al., 2006). However, this approach does not address the question of the constraints of the sensitive period during which LG can alter development. This question can be addressed by implementing the cross-fostering at later time points within the postnatal period. Recent studies have explored the impact of cross-fostering offspring between low- and high-LG rat dams on PND 6 and PND 10 to determine the period of sensitivity to postnatal LG (Pena et al., 2013) (see Fig. 2C). Cross-fostering at PND 6 was found to shift levels of ER $\alpha$  mRNA in the MPOA and maternal sensitivity of juvenile offspring toward the phenotype of the foster dam. Thus, offspring that had experienced low levels of LG up until PND 6 who were then cross-fostered to a high-LG dam had elevated levels of ER $\alpha$  in the MPOA and increased maternal sensitivity (compared to non-fostered siblings). The converse was observed in offspring initially reared by a high-LG dam; cross-fostering at PND 6 resulted in reduced levels of ER $\alpha$  mRNA in the MPOA and decreased maternal sensitivity (Pena et al., 2013). This alteration in ER $\alpha$  and maternal sensitivity is also observed through targeted manipulation of *Esr1* expression in the developing hypothalamus at PND 4. Over-expression of *Esr1* in the hypothalamus during this sensitive period results in increased ER $\alpha$  mRNA and protein in the MPOA and increased maternal sensitivity in offspring reared by low-LG dams (Pena and Champagne, 2015). However, sensitivity to LG appears to diminish by PND 10. Offspring reared initially by a low- or high-LG dam who were then cross-fostered to a high- or low-LG dam at PND 10 did not exhibit any change in ER $\alpha$  mRNA or maternal sensitivity (Pena et al., 2013). Similar to studies of olfactory conditioning, these developmental outcomes have limited plasticity in response to the maternal environment beyond PND 10, suggesting temporal constraints on the sensitive period for the effects of maternal care.

One of the caveats of the cross-fostering approach is that the utility of this method in determining the causal impact of maternal care on development is dependent on the assumption that maternal phenotype is not altered by the phenotype/genotype of pups. However, as has been demonstrated repeatedly in rearing and cross-fostering studies, offspring can exert considerable influence on the quality of care they receive. For example, spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats display divergent levels of maternal care, with SHR dams engaging in elevated levels of LG and nursing compared to WKY dams (Myers et al., 1989). However, when pups are cross-fostered on the day of birth between SHR and WKY dams, the maternal behavior of these dams shifts toward that of the pup strain. SHR dams caring for WKY pups display reduced levels of LG and nursing, whereas these behaviors are increased in WKY dams rearing SHR pups (Cierpial et al., 1990). In mice, though B6 dams typically show reduced levels of nursing behavior when compared to dams of the 129S strain, rearing fostered B6 pups abolishes these strain differences in maternal behavior (Curley et al., 2010). In the case of variation in LG, during the first week postnatal, group differences in maternal LG are maintained even when dams are rearing fostered pups (Champagne et al., 2003). However, the behavioral differences between low- vs. high-LG dams diminish across the postnatal period, due to overall decreases in both LG and pup nursing (Jensen Pena and

Champagne, 2013). Pup age is a significant predictor of the amount of maternal care received (Branchi et al., 2013) and the incentive value of the pups to the dam is significantly higher prior to PND 10 compared to later postpartum time points (Seip and Morrell, 2007). These changes in mother–infant interactions across time reflect the changing developmental needs of rodent pups and so it may be these naturally occurring shifts toward social and nutritional independence that shape the sensitive period to variation in maternal care.

## 5. Conclusions and future directions

Advances in our understanding of the mechanisms through which maternal care influences the developing brain have come through integration of both experimental and epidemiological studies and through analyses of behavioral, neuroendocrine, cellular, and molecular levels at which these influences manifest. Epigenetic changes have been demonstrated to be associated with the quantity and quality of maternal care experienced during development using a variety of experimental approaches that model both increases in and disruption to mother–infant interactions (Weaver et al., 2004; Champagne et al., 2006; Roth et al., 2009; Branchi et al., 2011). It is also clear, that there are sensitive periods for the impact of maternal care that are shaped by neurobiological and behavioral changes that accompany the transition to independence (Pena et al., 2013; Upton and Sullivan, 2010; Hess, 1959; Curley et al., 2009; Franks et al., 2015). However, these sensitive periods can be shifted or even re-opened through manipulation of neural systems involved in plasticity and it is certainly the case that epigenetic plasticity may continue throughout the lifespan (Weaver et al., 2004, 2005). It is also likely, that social experiences that characterize each developmental stage may have the capability to alter neurobehavioral development. Though mother–infant interactions may have a sensitive period that ends pre-weaning, characteristics of the weaning process, interactions with peers, and experiences during reproduction should also be considered as developmentally meaningful signals that can alter brain function and behavior.

Though our knowledge of the mechanisms through which maternal care shapes offspring development has certainly expanded, there are many areas within this field of study that hold significant promise for elucidating the process and temporal dynamics of this maternal influence. (1) *Timing of developmental and epigenetic changes.* Though there have been increasing efforts to include time course analysis of the effects of maternal care, the systematic use of this approach is needed across paradigms. Molecular changes that transduce the influence of maternal care may not necessarily overlap with those mechanisms that maintain the changes over the lifespan. Thus, without these temporal insights, conclusions regarding process will be difficult to make. Cross-fostering between dams that vary in maternal phenotype or limiting exposure to communal rearing or home-cage disruption to specific time-points may also be revealing regarding the timing and sensitivity to developmental change. (2) *Sex differences matter.* Converging evidence indicates the differential impact of early life experiences on long-term developmental outcomes in males vs. females (Kundakovic et al., 2013; Mueller and Bale, 2008; D'Andrea et al., 2010). Despite this knowledge, the assessment of both males and females in basic neuroscience and pre-clinical studies is relatively rare. Though both male and female offspring have been assessed in the experimental approaches used to study the influence of maternal care, comparison of the impact of mothers on males vs. females is not systematically employed. Epigenetic analyses suggest that males and females have a differential molecular response to disruptions in maternal care and yet there

is limited understanding of the factors that contribute to this sex difference. Policy changes may encourage the comparison of male and female offspring (Clayton and Collins, 2014), and perhaps allow for better integration of HPG development with epigenetic and neural systems influenced by maternal care. (3) *A complex maternal environment.* Though variation in maternal care, particularly within the low- vs. high-LG model, implicates the tactile components of mothering as a critical mediating variable, mother–infant interactions are complex and likely involve multiple pathways of influence. In addition to tactile stimulation and the formation of odor preferences, mothers can shape development via hormones transmitted during nursing (Hinde et al., 2015), thermoregulation during nursing (Jans and Woodside, 1990) and through influence on the microbiome (Daft et al., 2015). These maternal factors likely work collectively to shape development, interact with characteristics of the offspring, and create multiple possible developmental trajectories. (4) *Developmental age.* The quality of the early maternal/social environment may alter the pace of developmental change, thus adding an additional layer of complexity to the study of the timing of the effects of maternal care. The experience of low levels of maternal care is associated with early weaning and puberty onset (Cameron et al., 2008; Franks et al., 2015) and with accelerated maturation of fear systems (Callaghan and Richardson, 2011), which may reduce the duration of the sensitive period to maternal care. Thus, it may be necessary to focus not on the changes that emerge at a given chronological age across groups but rather to examine whether those changes emerge earlier or later as a function of the quantity or quality of mother–infant interactions – highlighting the importance of timing to better understand mechanism.

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